-- 43. A modified protein with enhanced avidity or affinity to a receptor, said modified protein comprising:

a first region capable of binding to said receptor; and

a linearly joined at least second region capable of binding to said receptor. --

REMARKS

Amendments to the Specification:

Pursuant to Examiner request (Office Action, item 15), applicants have amended the specification to correct minor clerical errors. The errors would be recognized as such by the skilled artisan; accordingly, no new matter has been added.

Amendments to the Drawings:

The Examiner has requested that the application be brought into compliance with the sequence listing rules, 37 C.F.R. §§ 1.821 - 1.825. In response, applicants request that the Examiner approve the proposed amendments to FIG. 2, shown in red on the enclosed drawing sheet, which add SEQ ID NOs.: for all sequences disclosed therein.

Further responsive to the Examiner's request, applicants file herewith a Sequence Listing for all sequences disclosed in the specification, including FIG. 2, and additionally file a Statement under 37 C.F.R. § 1.821(f) attesting to the identity as among specification and the Sequence Listing in paper and computer readable formats.

Amendments to the Claims:

In order more particularly to point and out distinctly claim the invention, applicants herein cancel claims 1 - 11 without prejudice and add new claims 12 - 43.

Claims 12 - 43 are thus presented for examination in the instant application. For the reasons set forth below, applicants submit that the amendments add no new matter.

Support for new claims 12 - 43 can be found throughout the specification, including drawings and claims as originally filed, and particularly as follows.

Support for new claims 12 and 27 can particularly be found in the Summary of the Invention on page 6, line 28 - page 7, line 5 and in the Introduction to the Present Invention on page 24, line 10 - page 3, line 6. Support for a region capable of binding to an FcRb receptor is found on page 25, line 13 - 25 and Figure 1A. Support for joining the at least second region is expressed throughout the specification as multimerized regions, page 26, lines 9 - 11, tandem regions, page 26, line 14, or physically linking at least one domain to a second domain, page 24, lines 29 - 34. The physical structure of linearly joined Fc regions is shown schematically in Figure 1B. The importance of the FcRb receptor in mediating the catabolism of IgG and especially in effecting the long serum half life of IgG compared to other molecules is described in the Background of the Technology on page 1, line 17 - page 6, line 12.

Support for FcRn, FcRb and FcRp receptors, as recited in claims 13 - 16 and claims 28 - 31, is found particularly on page 24, lines 10 -15 and in Example 5 on page 53, line 9 - page 57, line 7.

Support for the region that is capable of binding to an FcRb receptor being an Fc region, as recited in claims 17 and 32, can be found particularly on page 25, lines 1 -7 and in Figure 1.

Support for an IgG Fc region being capable of binding to an FcRb receptor, as recited in claims 18 and 33, is found particularly on page 25, line 1 - page 26, line 2 and in Figure 1B.

Support for the protein to be modified being an antibody, as recited in claims 19 and 34, is found particularly on page 25, lines 1 -20 and in Figure 1.

Support for the antibody being an antibody specific for IL-8, as recited in claims 20 and 35, is found particularly in Example 7 on page 58, lines 4 - 28.

Support for the antibody being an antibody that comprises an IgG heavy chain, as recited in claims 21 and 36, is found particularly on page 22, lines 18 - page 24, line 8.

Support for the antibody comprising a dimer, as recited in claims 22 and 37, is found particularly on page 22, line 18 - page 23, line 14.

Support for the antibody being a human antibody, as recited in claims 23 and 38, is found particularly on page 31, line 8 - page 32, line 26.

Support for joining being by recombinant fusion technology, as recited in claims 24 and 39, is found particularly on page 25, lines 1 - 20.

Support for the at least second region being joined to the C-terminus of the first region, as recited in claims 25 and 40, is found particularly in FIG. 1B.

Support for the first and at least second regions being identical, as recited in claims 26 and 41, can be found particularly on page 26, lines 9 - 22.

Support for a modified protein having a first and at least second region capable of binding to an FcRb receptor, the modified protein having a serum half life in mammals greater than the unmodified protein, as recited in claim 27, can be found throughout the specification and particularly on page 27, lines 7 - 27; Example 2, page 59, lines 13 - 32; and in Figure 3.

Support for enhancing the avidity or affinity of a protein to a receptor, said protein having a first region capable of binding to said receptor, the method comprising joining at least a second region capable of binding to the receptor, as recited in claim 42, can be found particularly on page 28, line 14 - page 31, line 6. Support for a protein so modified, as recited in claim 43, is also found with particularity on page 28, line 14 - page 31, line 6.

Oath or Declaration:

The Examiner states that the oath or declaration is defective for failure correctly to claim priority to the Provisional Application referenced in the specification's cross-reference to related applications.

The instant application No. 09/375,924, filed August 17, 1999, claims priority to Provisional Application No. 60/096,868, filed August 17, 1998.

In response to the Notice to File Missing Parts dated September 3, 1999, applicants timely filed in counterpart two signed Declarations and Powers of Attorney claiming priority to Provisional Application No. 60/096,868. Applicants are unable to identify the alleged deficiency in

the executed declarations. Applicants believe they have properly claimed priority under 35 U.S.C. 119(e) in accordance with 37 C.F.R. 1.67(a), and respectfully request that the Examiner withdraw the objection. Should the Examiner still find the oath to be defective, applicants invite the Examiner to call the undersigned to expedite any required correction.

Rejections under 35 U.S.C. § 112, ¶ 2 Are in Error, Have Been Obviated, and Should be Withdrawn

The Examiner rejects claims 1-11 under 35 U.S.C. § 112, paragraph 2, as being indefinite in the recitation of "FcRn binding," "because it is not clear what this term encompasses." Office Action, page 2.

The language found objectionable by the Examiner is part of a longer phrase, "FcRn binding domain", which is clearly and distinctly described in the specification.[1] In light of this explicit definition in the specification, applicants respectfully submit that those skilled in the art would understand what is claimed through use of the phrase "FcRn binding domain". "Because the claims reasonably appraise those skilled in the art both of the utilization and scope of the invention, and because the language is as precise as the subject matter permits, the claims are not invalid for indefiniteness." *PPG Industries, Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618, 1622 (Fed. Cir. 1996) (internal quotations and citations omitted).

However, solely to expedite prosecution, the applicants have replaced the phrase with "region capable of binding to the FcRb receptor" in the claims newly added by amendment herein.

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[1] *See, e.g.*, specification page 25, lines 1 - 7; page 25, line 33 - page 26, line 2; page 26, lines 26 - 28; page 24, line 10 - page 27, line 27; page 28, lines 14 - 17.

For the foregoing reasons, the rejection under 35 U.S.C. § 112 paragraph 2 is in error and has been obviated and should thus be withdrawn.

Rejections Under 35 U.S.C. § 102(a) Have Been Obviated and Would be in Error if Asserted Against the Claims Newly Added by Amendment Herein

The Examiner rejects claims 1 - 4, 6, 7, 9 and 11 under 35 U.S.C. § 102(a) as anticipated by Junghans, WO 97/43316 (hereinafter "WO 97/43316"); claims 5 and 10 are recognized to be novel over the cited art. The rejection has been obviated by cancellation of all pending claims. For the reasons advanced below, applicants further submit that the rejection would be in error if reasserted against the claims newly added by amendment herein.

WO 97/43316, citing Burmeister *et al.*, *Nature* 372:379-383 (1994), teaches that several sites within the IgG molecule, collectively termed the Brambell motif, are involved in binding to the FcRp receptor,[2] and further teaches the modification of native molecules to include the disclosed sequences and sequences homologous thereto. Modification is said to result in increased serum half life.[3]

The Examiner bases the instant rejection in part on the "teach[ing] that the FcRp and FcRn are the same receptor." Office Action p. 3. Applicants acknowledge the equivalence of the FcRp, FcRn and FcRb receptors. *See* R.P. Junghans,

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[2] " . . . amino acid residues 248 to 257 (KTLMISRTP); amino acid residue 272 (E); amino acid residue 285 (H); amino acid residue 288 (K); amino acid residue 314 (L:); amino acid residues 385 to 387 (GQP); amino acid residue 428 (M); and amino acid residues 433 to 436 (HNHY)." WO 97/43316 page 7, line 30 - page 8, line 1.

[3] WO 97/43316, page 3, lines 8 - 10.

Immunologic Research, 16:29-57 (1997) at 45, column 2,[4] and applicants' specification at page 24, line 12; page 27, line 31; and page 27, line 35. The novelty of applicants' invention lies not in any perceived qualitative difference as among FcRp, FcRn and FcRb receptors, but rather in the quantitative number of FcRb/FcRn/FcRb-binding regions present in applicant's modified molecules.

Claims 12 and 27 as newly added by amendment herein recite:

> 12. A method of extending the serum half life of a protein having a first region capable of binding to an FcRb receptor, the method comprising:
> joining to said protein at least a second region capable of binding to an FcRb receptor.
>
> 27. A modified protein with an extended serum half life, said modified protein comprising:
> a first region capable of binding to an FcRb receptor; and
> at least a second region capable of binding to an FcRb receptor.

WO 97/43316 does not teach the joining to a molecule that has a first region capable of binding to an FcRb receptor at least a second such region. Rather, WO 97/43316 teaches that

> the physiologically active molecules, e.g., proteins and peptides, of the invention can be modified as described herein to include at least a portion of an amino acid sequences [*sic*] which is substantially homologous, e.g., at least about 60%, 70%, 80%, 90%, 95%, 98%, or 99% homologous, to an amino acid sequence, e.g., the Brambell motif, of at least a

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[4] "This [FcRb knockout] lesion knocking out protection as well as transport thus provided the final genetic and functional link to support the identity of these two molecules . . ., FcRp and FcRn, and their unification as the Brambell receptor [FcRb]."

> portion of the IgG domain which binds to the IgG protection receptor FcRp.[5]

Modification is by amino acid substitution — "[t]hese methods include altering the amino acid sequence of the protein or peptide by amino acid substitution such that the protein or peptide specifically binds to the IgG protection receptor FcRp"[6] — not by addition of sequence.

"To be anticipating, a prior art reference must disclose each and every limitation of the claimed invention, must be enabling, and must describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *Helifix Ltd. v. Blok-Lok Ltd.*, 54 USPQ2d 1299, 1303 (Fed. Cir. 2000) (quoting *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994)). Failing to teach the joining of at least a second region capable of binding to an FcRb receptor to a molecule that has a first such region, WO97/43316 cannot anticipate applicants' claimed invention; the rejection would, therefore, be in error if asserted against the claims newly added by amendment herein.

Rejections Under 35 U.S.C. § 103(a) Have Been Obviated and Would Be in Error if Reasserted Against Claims Newly Added by Amendment Herein

The Examiner rejects claims 1-11 under 35 U.S.C. § 103 as obvious over three separate combinations of references. The rejections have been obviated by cancellation of all pending claims. For the reasons advanced below, the rejections would be in error if reasserted against the claims newly added by amendment herein.

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[5] WO 97/43316, p. 8, lines 1 - 11 (emphasis added).

[6] WO 97/43316, p. 4, lines 9 - 11.

To meet its threshold burden of establishing a *prima facie* case of obviousness, *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992), the PTO must first establish the scope and content of the prior art, *Graham v. John Deere Co.*, 383 U.S. 1, 17 - 18; M.P.E.P. § 2141. In two of the three rejections under 35 U.S.C. § 103, the Examiner has misconstrued the teachings of two of the primary references, and has thus failed to establish the factual predicate to a *prima facie* case of obviousness. In the third of the rejections, the primary reference is factually irrelevant to the claimed invention, again vitiating the Examiner's *prima facie* case. In the absence of a valid *prima facie* case of obviousness, the rejection would be in error if reasserted against the claims newly added by amendment herein.

Junghans in view of Doerschuk *et al.*,
Ladner *et al.*, Junghans, and Braxton

In a first rejection under 35 U.S.C. § 103(a), the Examiner rejects claims 1-11 as having been obvious over Junghans (WO 97/43316) in view of Doerschuk *et al.* (U.S. Patent No. 5,702,946), Ladner *et al.* (U.S. Patent No. 4,946,778), Junghans (*Immunologic Research*, 1997, Vol. 16:29-57) and Braxton (U.S. Patent No. 5,766,897).

In describing Junghans, the Examiner equates several short amino acid sequences within the CH2 and CH3 domains of IgG with "FcRn binding domains", and from that definitional identity argues that "Junghans teaches a modified antibody which has an extended half-life in a subject . . . comprising at least a first and second FcRn binding domain physically linked to a constant region of the antibody (especially claims 1, 5, 6 10 and Table 1)." Office Action p. 4.

The identified sequences indeed **contribute** to the binding of IgG Fc to FcRn/FcRp. See, *e.g.*, Zuckier *et al.*, "Chimeric human-mouse IgG antibodies with shuffled constant

region exons demonstrate that multiple domains contribute to in vivo half-life," *Cancer Res.* 58(17):3905-3908 (1998). There is neither teaching nor suggestion in Junghans, however, that any one such sequence is alone sufficient to mediate such binding. In contrast, applicants' claimed invention requires the presence of a multiplicity of regions, **each of which** is alone capable of mediating binding to the FcRb ("a first region capable of binding to an FcRb receptor" and "at least a second region capable of binding to an FcRb receptor").

As noted above, which discussion is incorporated here by reference, Junghans teaches modification of amino acid sequence, rather than its addition. Where modification is proposed of native antibodies, the classes and subclasses proposed to be modified are explicitly those that bind poorly, if at all, to FcRp: "IgG3, IgA, IgD, IgE and IgM." Junghans page 4, lines 11 - 13; Junghans claims 6, 9, 24, and 27. Nowhere does Junghans suggest that modification could usefully be the addition of at least a second region capable of binding FcRb to a molecule, such as an antibody of IgG1, IgG2a, or IgG2b subclass, that has a first region capable of binding efficiently to an FcRb receptor.

The secondary references do not satisfy the deficiency of the primary reference. Doerschuk *et al.* discloses the utility of anti-IL-8 monoclonal antibodies in treating inflammatory disorders. Ladner *et al.* discloses the general advantages of single chain antibodies. Braxton discloses the well-recognized need to increase the half-life of serum proteins for developing more effective protein therapies. Junghans reviews the history and present status of research into the FcRb.

Having misconstrued the teachings of the primary reference, the Examiner has failed to establish the factual predicate to a *prima facie* case of obviousness. Without more, applicants are entitled to withdrawal of the rejection. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("If

examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent.").[7]

Presta *et al.* in view of Doerschuk *et al.*, Ladner *et al.*, Kallos *et al.* and Braxton

In a second rejection under 35 U.S.C. § 103(a), the Examiner rejects claims 1-11 as having been obvious over Presta *et al.* (WO 96/32478) in view of Doerschuk *et al.* (U.S. Patent No. 5,702,946), Ladner *et al.* (U.S. Patent No. 4,946,778), Kallos *et al.* (*Prog. Allergy*, Vol. 13, 1969, pages 1-109) and Braxton (U.S. Patent No. 5,766,987).

The Examiner argues that "Presta *et al.* teach a method of modifying the half-life of . . . proteins comprising recombinantly linking more than one FcRn binding domain (see entire document)", Office Action p. 6. Applicants respectfully disagree.

Rather than teaching the addition of at least a second region capable of binding to the FcRb receptor to a protein having a first region capable of binding to the FcRb, Presta *et al.* instead teach the modification of native epitopes to include amino acid sequences identical or homologous to the amino acid sequences of an IgG known to bind to "salvage receptors":

> [t]he variants of the polypeptide of interest . . . include, for example, deletions from, insertions or substitution of, residues within the amino acid

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[7] Applicants reserve the right, should the Examiner reassert the rejection based upon a correct reading of Junghans, further to challenge the motivation or suggestion to combine the cited references, a further prerequisite to the Examiner's *prima facie* case, *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999); *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), and reserve the right to rebut any *prima facie* case that may thereafter deemed established.

> sequence of the polypeptide of interest so that it contains the proper epitope and has a longer half-life in serum. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics.[8]

Nowhere do Presta *et al.* teach the joining of at least a second region capable of binding to the FcRb receptor to a protein having a first region capable of binding to the FcRb.

Quite to the contrary, Presta *et al.* teach away from applicants' invention, taking great and explicit pains to exclude molecules that have a plurality of regions capable of binding to FcRb. Thus, Presta *et al.* claim 1 explicitly recites (with emphasis added):

> 1. A polypeptide variant of a polypeptide of interest <u>which polypeptide</u> of interest is cleared from the kidney and <u>does not contain a Fc region of an IgG</u>, which variant comprises a salvage receptor binding epitope of an Fc region of an IgG, and which variant has a longer *in vivo* half life than the polypeptide of interest.

The Presta *et al.* specification is in accord. *See* page 2, lines 16, 28 and 35 - 36; and claims 27 and 29.

The secondary references do not satisfy the deficiency of the primary reference. Doerschuk *et al.* disclose the utility of anti-IL-8 monoclonal antibodies in treating inflammatory disorders. Ladner *et al.* disclose the general advantages of single chain antibodies. Kallos *et al.*[9] is an early review of antibody catabolism. Braxton discloses

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[8] Presta *et al.*, page 13, lines, 15 - 20.

[9] The reference is more properly described as **<u>Waldmann *et al.*</u>**, "Metabolism of Immunoglobulins," *Progr. Allergy* 13:1 - 110 (1969); Kallos is one of two editors of the volume. For consistency with the office action, however, applicants will refer to the reference as Kallos *et al.* herein.

the well-recognized need to increase the half-life of serum proteins for developing more effective protein therapies.

Having misconstrued the teachings of the primary reference, the Examiner has failed to establish the factual predicate to a *prima facie* case of obviousness. Without more, applicants are entitled to withdrawal of the rejection. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent.").[10]

Pastan *et al.* in View of Doerschuk *et al.*, Ladner *et al.*, Kallos *et al.* and Braxton

In a third rejection under 35 U.S.C. § 103(a), the Examiner rejects claims 1 - 11 as having been obvious over Pastan (WO 94/04689) in view of Doerschuk *et al.* (U.S. Patent No. 5,702,946), Ladner *et al.* (U.S. Patent No. 4,946,778), Kallos *et al.* (*Prog. Allergy*, Vol. 13, 1969, pages 1-109) and Braxton (U.S. Patent No. 5,766,987). Applicants respectfully traverse the rejection.

The Examiner characterizes Pastan *et al.* as "teach[ing] fusion proteins comprising toxins and the Fc region of IgG, preferably CH2, in order to increase serum half life and methods of making the fusion proteins," Office Action p. 7. The Examiner particularly cites several sections of the reference, reproduced below.

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[10] Applicants reserve the right, should the Examiner reassert the rejection based upon a correct reading of Presta *et al.*, further to challenge the motivation or suggestion to combine the cited references, a further prerequisite to the Examiner's *prima facie* case, *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999); *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), and reserve the right to rebut any *prima facie* case that may thereafter be deemed established.

> The present invention relates to the production and use of recombinant toxins modified to increase their half-life and thereby increasing their potency during therapy. More particularly, this invention relates to the use of regions of the Fc portion of an immunoglobulin molecule to confer an increased half-life on single chain chimeric toxins that include a ligand binding domain such as from CD4 receptor and a cytotoxic domain such as from *Pseudomonas exotoxin* A.[11]
>
> JKB-1 and JKB-2 . . . were used to generate the full length IgG constant region fragments by polymerase chain reaction (PCR) using human IgG1 cDNA as template. From this constant region, using the remaining primers the Fc immunoglobulin fragments CH2, CH3, CH1-CH2 and CH2-CH3 were generated that were then positioned between CD4 and PE 40 as illustrated in Figure 1B.[12]
>
> This invention relates to single chain recombinant proteins, comprising the following domains: (a) a cytotoxic domain; (b) a ligand binding domain; and (c) a peptide linking domains (a) and (b) comprising an IgG constant region domain having the property of increasing the half-life of the protein in mammalian serum. Preferably the IgG constant region domain is CH2 or a fragment thereof.[13]

Nowhere does Pastan *et al.* disclose, teach or suggest modifying proteins having a first domain capable of binding FcRb by joining thereto at least a second region capable of binding FcRb; Pastan *et al.* is thus completely irrelevant to applicants' claimed invention.

The secondary references do not satisfy the deficiency of the primary reference. Doerschuk *et al.* disclose the utility of anti-IL-8 monoclonal antibodies in treating inflammatory disorders. Ladner *et al.* disclose the general advantages of single chain antibodies. Kallos *et al.*

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[11] Pastan *et al.*, Abstract.

[12] Pastan *et al.*, p. 12, lines 11 - 17.

[13] Pastan *et al.* p. 3, line 35 - p. 4, line 3.

is an early review of antibody catabolism. Braxton discloses the well-recognized need to increase the half-life of serum proteins for developing more effective protein therapies.

With Pastan *et al.* neither disclosing, teaching, nor even suggesting applicants' claimed invention, the Examiner's *prima facie* case must fail. Without more, applicants are entitled to withdrawal of the rejection. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent.").[14]

For the foregoing reasons, applicants respectfully submit that the outstanding rejections under 35 U.S.C. have been obviated, that reassertion of the rejections against the claims newly added by amendment herein would be error, and that the rejections should be withdrawn.

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[14] Applicants reserve the right, should the Examiner reassert the rejection based upon other evidence adduced from Pastan *et al.*, further to challenge the motivation or suggestion to combine the cited references, a further prerequisite to the Examiner's *prima facie* case, *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999); *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), and reserve the right to rebut any *prima facie* case that may thereafter be deemed established.

CONCLUSION

Applicants respectfully submit that all outstanding objections and rejections have either been obviated or are in error, and should thus be withdrawn, and that the claims as amended herein are in good and proper form for allowance.

If the Examiner believes, however, that any issues remain outstanding and might be resolved more expeditiously by means of a telephone conference, applicants invite the Examiner to call the undersigned.

Respectfully submitted,

16 AUG 2000

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